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**REMARKS**

The present application was originally filed with 31 Claims. In a Restriction Requirement mailed October 2, 2003, the Examiner restricted the Claims into five Groups, with Group I containing Claims 1-6, 11, 14-29, and 31, directed to methods and systems for creating libraries of nucleic acid sequences; Group II containing Claim 7, directed to a library; Group III containing Claims 8, 9, and 30, directed to methods for screening libraries for a protein with an increase in a property of interest; Group IV containing Claim 10, directed to a protein; and Group V containing Claims 12 and 13, directed to methods for improving a desired parameter of a protein of interest. In a Response filed October 20, 2003, Applicants elected the Claims in Group I (Claims 1-6, 11, 14-29, and 31), with traverse, cancelled Claims 8-10, 12, 13 and 30 without prejudice. Thus, Claims 1-7, 11, 14-29 and 31 were pending in the present application.

In the present Final Office Action, the Examiner indicates that Claim 11 "... is drawn to an invention non-elected with traverse in the reply filed on 03 November 2003." (Final Office Action, page 3). Applicants must respectfully disagree, as Claim 11 is included in Group I, both in the Restriction Requirement and in the Response filed 3 November 2003. Thus, Applicants have not cancelled Claim 11 and believe that it is correctly included in the present application. However, as the Examiner has indicated that Group II (Claim 7) has not been joined with Group I (Claims 1-6, 11, 14-29 and 31). Claim 7 has been properly cancelled without prejudice in the present Response. Applicants reserve the right to pursue the original and/or broader and/or narrower Claims in additional application(s). Applicants appreciate the Examiner's withdrawal of previous objections/rejections not included in the present Final Office Action. The Examiner's rejections are addressed in the following order:

- 1) Claims 11, 23 and 24 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite; and
- 2) Claims 1-6, 11, 14-29, and 31 stand rejected under 35 U.S.C. §102(b), as allegedly being anticipated by Marr et al. (US Pat. No. 5,701,256).

**1) The Claims Are Definite**

The Examiner has rejected Claims 11, 23 and 24, under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. In particular, the Examiner indicates that Claim 11 is indefinite for failing to include a final process step which agrees back with the preamble. Applicants appreciate the Examiner's suggestions regarding the need for clarity and have

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amended the Claims to provide more clarity. No new matter is added in these amendments, as they find support throughout the Specification.

In regards to Claims 23 and 24, the Examiner argues that it is confusing how the probability matrix, constraint vector and algorithm are related. Applicants note that Claim 24 has been cancelled and assume that the Examiner's arguments pertain to Claim 25. Applicants appreciate the Examiner's suggestions, but respectfully submit that it is not necessary to specifically recite an algorithm in these Claims, as any equation known and used in the art to calculate probability matrices and any equation known and used in the art to calculate constraint vectors finds use in the present invention. Applicants respectfully submit that their Claims should not be limited to the specific embodiments set forth in the Specification. As the Claims are definite, Applicants respectfully request that this rejection be withdrawn.

### 3) The Claims are Novel

The Examiner has rejected Claims 1-6, 11, 14-29, and 31 under 35 U.S.C. §102(b), as allegedly being anticipated by Marr *et al.* (US Pat. No. 5,701,256; "the Marr *et al.* Patent"). The Examiner argues that the search information generated using the methods of the Marr *et al.* Patent is "...then transferred to a DNA library for construction (Columns 12-14, beginning on line 63)." (Office Action, page 6). Applicants must respectfully disagree, as the Marr *et al.* Patent simply indicates that the search methods provided by the Marr *et al.* Patent may be used to search libraries. In contrast to the Examiner's arguments, the particular column reference referred to by the Examiner does **NOT** indicate that "... such information is transferred to a DNA library for construction (Columns 12-14, beginning on line 63)." (Office Action, page 4). The passage referred to by the Examiner states (verbatim):

It is understood that user interface 25 and working routine 21 may be designed and coded (programmed) in several ways. The fundamental workings of the user interface 25 and working routine 21 are described above, bearing in mind that implementation specific details are within the purview of one skilled in the art. To that end, the foregoing description corresponding to **FIG. 2** is for purposes for illustration and not limitation of the present invention.

Further it is understood that the present invention enables routine searching at multiple PAMs and various gap penalties on relatively inexpensive workstations (as opposed to massively parallel computers with thousands of processors).

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Also the present invention works well for DNA or cDNA searches at the 15% error level (allowing gaps). The same user interface provides for protein or DNA searches (many-to-one alignment), multiple alignment, degenerate PCR (multiple protein fragments against DNA or cDNA databases), DNA sequencing contigs, and physical maps of clone libraries such as a map of fission yeast.

Other interfacing between the present invention and analytical tools and the like are understood to be in the purview of one skilled in the art.

Applicants respectfully submit that the Examiner may have misunderstood the text of these columns, as the passage provided above from column 12 line 63 through column 14, line 8, does not even mention libraries other than in the context of searching clone libraries. Applicants respectfully submit that there is absolutely **no** teaching of the transfer of information to a DNA library for construction in the passage cited by the Examiner. Furthermore, there is absolutely no teaching of the *generation* of libraries, in particular libraries in which substitutions of interest are incorporated into the libraries, anywhere in the Marr *et al.* Patent, let alone in columns 1-4, as indicated by the Examiner. As clearly indicated throughout the Marr *et al.* Patent, the methods of the Marr *et al.* Patent are suitable for **searching** libraries. The methods of the Marr *et al.* Patent find use in identifying substitutions in sequence, but are not useful in the actual generation of libraries containing these substitutions. Thus, Applicants respectfully submit that the Marr *et al.* Patent does not teach nor even remotely suggest how to generate libraries. Thus, Applicants respectfully request that this rejection be withdrawn and the Claims passed to allowance.

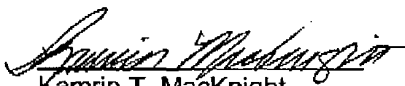
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**CONCLUSION**

All grounds of rejection and objection of the Final Office Action of June 25, 2004, having been addressed, reconsideration of the application is respectfully requested. Applicants respectfully submit that the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-5838.

Respectfully submitted,

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